Appl. No. : 08/484,594
Filed : June 7, 1995

Remarks

Claims 12, 14, 18, 22 and 23 have been amended. Accordingly, Claims 12-25 remain presented for examination. Applicants and Applicants' representative wish to thank Examiners Hayes and Allen for the courteous personal interview conducted on May 7, 1997. In that interview, the undersigned discussed with the Examiners proposed amendments and arguments believed to advance the case toward allowance. The substance of the interview is incorporated into the foregoing amendment and the following remarks. Support for the recitation of ischemic nerve injury and traumatic nerve injury in Claim 14 may be found at page 8, lines 15-20 of the specification. Reconsideration and withdrawal of the present rejections in view of the amendments and arguments presented herein are respectfully requested.

Objection to the disclosure

The PTO objected to the disclosure, stating that Claim 22 now recited "[a] method for *of treating*..." Appropriate correction has been made.

Discussion of rejection under 35 U.S.C. §112, first paragraph

As an overview of the data of record and the enabling language present in the specification, please consider the following Table 1. The import of the data in the table in demonstrating compliance with 35 U.S.C. §112, first paragraph, is discussed in more detail below.

D

Appl. No. : 08/484,594
Filed : June 7, 1995

Table 1

Reference/ exhibit	Effect	Dosage	Dosage in specification	Route of admin.	Route in specification
Exhibit E (Kotani et al.)	Prevention of ischemia-induced learning disability and hippocampal neuronal loss *in vivo*	0.25 μg/kg	0.01-100 μg/kg	Direct local infusion into brain	Direct local admin. p. 10, line 8; p. 11, line 14; p. 22, lines 8-12
Hozumi et al.	Improvement in spatial learning impairment after bilateral stab wounds in brian cortices and hippocampi *in vivo*	1 μg/kg	1-10 μg/kg	Direct local infusion into brain wound	Direct local admin. p. 10, line 8; p. 11, line 14; p. 22, lines 8-12
Exhibit G (diabetic neuropathy)	Improvement in diabetes-induced sensory neuropathy *in vivo*	20, 200 & 1,000 μg/kg	0.1-1000 μg/kg	Systemic injection	IV injection p. 10, line 17
Exhibit H (taxol neuropathy)	Improvement in taxol-induced sensory neuropathy *in vivo*	200 μg/kg	0.1-1000 mg/kg	Systemic injection	IV injection p. 10, line 17
Exhibit I (MNCV and SNCV)	Improvement in nerve conduction velocities *in vivo*	200 & 1,000 μg/kg	0.1-1000 μg/kg	Systemic injection	IV injection p. 10, line 17
Exhibit D Sano et al.	Prevention of ischemia-induced learning disability and neuronal loss *in vivo*	~3.2 μg/kg	1-10 μg/kg	Local infusion into lateral ventricles	Local admin p. 10, line 8; p. 11, line 14; p. 22, lines 8-12
Exhibit F (Kotani et al.)	Regeneration of sciatic nerve *in vivo*	0.03 μg/kg	0.01-100 μg/kg	Local injection	Local admin. p. 10, line 13-15

Appl. No. : 08/484,594
Filed : June 7, 1995

The PTO rejected Claims 12-25, maintaining the nonenablement rejection set forth in the previous Office Action. The PTO questioned the operability of the claimed invention and whether the specification was commensurate in scope with the claims, which included "preventing" or slowing the progress of disease. The claims as amended recite "inhibiting" demyelination and neural degeneration which has clearly been shown in the specification and supporting data submitted in Applicants' last response. In addition, Claim 14 has been amended to recite multiple sclerosis, traumatic injury and ischemic injury. These proposed claim amendments were favorably received at the interview.

The operability requirement is satisfied if operability is believable to a person of ordinary skill in the art. If a *prima facie* case of nonoperability is shown, it must be reassessed in light of all subsequently-submitted evidence to determine whether in would be believable in view of all the evidence of record. Post-filing date animal models showing that the inventor correctly identified an operable invention need not themselves have been enabled in the specification; all that is required is that the **claimed** method be enabled. As discussed below and summarized Table 1, the specification describes preferred dosages that are operable, within a single order of magnitude, as later confirmed *in vivo* by the published literature. The literature and declaration evidence also show operability within the broader dosage range disclosed in the specification. Operable routes of administration have also been shown. The standard of operability under § 112 is not particularly high. The enabled invention need not be optimized; it need not work better than the prior art; and it need not be in commercial form.

Indeed, so long as it works even to a small degree, the requirement is satisfied. A "cure" is not required unless so specified by the claims.

The evidence of record and the evidence submitted herewith clearly support findings of both enablement and operability. The Examiner asserted that without sufficient neural structure there can be no function. However, Exhibit E of Applicants' previous declaration (Kotani et al., *J. Neurochem.*, 66:2197, 1996) showed that the saposin C-derived peptide prevented ischemia-induced learning disability and hippocampal neuronal loss *in vivo*. The enclosed abstract by Hozumi et al. (Intl. Soc. Neurochem, Boston, 1997) shows that prosaposin, when injected directly into bilateral stab wounds in cortices and hippocampi, resulted in significant improvement in wound-induced spatial learning impairment compared to control animals. Further, the enclosed second Declaration of John O'Brien, M.D., states that neural function can be retained even if up to 90% of spinal cord motor neurons and up to 97% of dopaminergic neurons are lost (Decl., ¶5). Thus, significant neural structure can be lost while retaining function.

This post-filing date data discussed above is not being relied upon to provide enabling disclosure. These references instead confirm that the invention works as described in the specification. The specification at page 10, lines 17-19 lists the following routes of administration: intravenous, intramuscular, intradermal, subcutaneous, intracranial, epidural, topical and oral. The specification at page 10, lines 33-34 states that daily systemic dosages are 10-100 μg/kg, although dosages of 0.1-1,000 μg/kg are contemplated. Page 10, lines 35-36

state that daily dosages of locally administered material will be about an order of magnitude less (i.e. 1-10 μg/kg preferred; 0.01-100 μg/kg also contemplated).

In the gerbil ischemia-induced learning disability model, 20 ng peptide/day was locally infused into the brain. The animals weighed 70-80 g each. This translates to a dosage of 0.25 μg/kg which is within the range stated in the specification. In the rat stab wound model, 240 ng prosaposin was infused into the wound for three days. Assuming that an average rat weighs 250 g, this translates to about 1 μg/kg, exactly at the lower end of the preferred range disclosed in the specification for local delivery. A person of ordinary skill in the art would likely start at the lower end of the range, and with no experimentation would have an "effective amount." In the rat diabetic neuropathy model (Exhibit G of previous Declaration), systemic peptide dosages of 20 μg/kg, 200 μg/kg and 1,000 μg/kg all showed efficacy. In the taxol-induced neuropathy model (Exhibit H of previous Declaration), a systemic peptide dosage of 200 μg/kg was efficacious. In the nerve conduction velocity studies (Exhibit I of previous declaration), systemic peptide dosages of 200 μg/kg and 1,000 μg/kg showed efficacy. In Exhibit D of the previous Declaration (Sano et al.), prosaposin was shown to prevent ischemia-induced learning disability and neuronal loss in gerbils when infused into the lateral ventricles at a dosage of about 3.2 μg/kg. See Table 1. In Exhibit F of the previous Declaration (Kotani et al.), regeneration of rat sciatic nerve was observed after local administration of prosaposin at 0.03 μg/kg. These overlap the narrow preferred systemic range and are also fully within the range disclosed in the specification.

Appl. No. : 08/484,594
Filed : June 7, 1995

Sufficient evidence has been presented to support claims to treating demyelination and inhibiting neural or myelin degeneration. As shown in Exhibit A of the previous Declaration, the peptide inhibits Schwann cell death. The enclosed references by Talley et al. (*Mol. Cell. Biol.*, **15**:2359-2366, 1995) and D'Souza et al. (*J. Neurosci.*, **15**:7293-7300, 1995) show that TNF-α induces apoptosis (cell death) in human neuronal cells. The enclosed paper by Vartanian et al. (*Molecular Med.*, **1**:732, 1995) states that IFN-γ is a potent inducer of oligodendrocyte apoptosis and that oligodendrocyte apoptosis was observed at the advancing margins of chronic active multiple sclerosis (MS) plaques. This reference also states that IFN-γ plays a role in the pathogenesis of MS by activating apoptosis in oligodendrocytes. See abstract. As stated in the second Declaration of John O'Brien, enclosed herewith, the peptide also inhibits both TNF-α- and IFN-γ-induced oligodendrocyte cell death (second Decl., ¶3). These two cell types are responsible for maintaining the myelin sheath. If these cells degenerate, myelin is lost. Because the peptides prevent death of these myelin-maintaining cells, they necessarily prevent demyelination.

As shown in Exhibit B of the previous Declaration, the peptide upregulated the synthesis of sulfatide and stimulation of ^{35}S incorporation in cultured Schwann cells. As stated in the second declaration, sulfolipids are an accepted marker for myelination. The peptides also completely prevented the loss of large myelinated fiber nerve mass in the rat diabetic neuropathy model (second Decl., ¶4). In addition, as shown in the enclosed publication of Misasi et al. (*Glycoconjugate J.*, **13**:195-202, 1996), the peptides induced significant increases in three major ganglioside constituents of neuroblastoma cells in culture.

As discussed in the enclosed *Science* meeting brief (Barinaga, 274:1466, 1996), spinal cell death continues for up to 3 weeks post-injury. Cells die not from damage due to the blow itself, but from apoptosis. Among the cells that die are oligodendrocytes. It is becoming well accepted that apoptosis blockers may limit spinal cord injuries. This opens a longer window of opportunity for therapy. Prosaposin, saposin C and peptides derived therefrom containing the active neurotrophic region block this apoptosis, as described above, and thus inhibit apoptosis-induced demyelination.

This recent understanding of the mechanism of action of prosaposin merely provides a confirmatory scientific explanation of what the specification has taught all along - specifically, that prosaposin and active fragments exert a neuroprotective effect when administered as indicated in the specification. Note that an inventor need not know why the invention works - only how to make and how to use the invention.

In his previous Declaration, Dr. O'Brien correctly stated that *in vitro* results in the neuroscience field were predictive of *in vivo* efficacy. This has been borne out by the data of record and additional data enclosed herewith. The *in vitro* results disclosed in the specification were predictive of the *in vivo* results observed in both the gerbil ischemia-induced learning disability and rat stab wound models discussed above. In addition, Kotani et al. also correlated *in vitro* with *in vivo* results.

The reference cited by the PTO regarding the feasibility of intracerebral administration of neurotrophic factors (Hefti et al., *Neurobiol. Aging*, 9:689-690, 1988) is actually supportive of the claimed invention. Hefti et al. note the success of osmotic minipumps in intracerebral

administration of neurotrophic factors to rodents, and suggests possible improvements that could make intracerebral administration to humans more convenient. The abstract acknowledges successful intracerebral administration of NGF, and says that such intracerebral administration "may become a generally valuable approach . . .." It then "briefly discusses possible strategies for the development of such 'neurotrophic factor treatments.'" Those strategies are entirely consistent with the present invention, and include use of active fragments and infusion pumps, exactly as disclosed in the specification. A person of ordinarly skill in the art, in light of this reference, would find intracerebral administration to be a practical and believable methodology. Indeed, therapeutic agents are now routinely administered to the CNS (i.e. Medtronic infusion pumps, epidural blocks given to women in labor or for lower body surgery). Although blood brain barrier data are already of record, Applicants are not required to show that prosaposin will readily cross the blood brain barrier because alternative modes of administration are disclosed in the specification which do not require this process.

The PTO's statement that nerve cells do not regenerate is incorrect. As shown in the enclosed reference (Kempermann et al., *Nature*, **386**:493, 1997), neuritogenesis in the hippocampus occurs throughout the lifetime of vertebrates. However, the PTO's statement is irrelevant because the claims at issue do not require nerve cell regeneration of curing a neural or myelination disorder. Nor is it necessary for Applicants to show complete recovery from neural damage for the claimed method to be operable. Thus, demonstration of a return to non-diabetic control values for the nerve conduction velocity and neuropathy data presented in the

previous declaration is not required. The demonstration of significant improvement compared to the controls clearly exceeds the legally-required degree of efficacy.

Finally, Applicants need not disclose how to initiate clinical trials. At most, the specification needs to enable only the identity of the compound, the condition being treated, an operable route of administration, and either an operable dosage range or a screening procedure. All of these requirements are satisfied in the specification as originally filed.

In view of the amendments and arguments presented above, and the favorable reception given these points at the interview, Applicants respectfully request withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

Applicants submit that all claims are in condition for allowance. However, if minor matters remain, the Examiner is invited to contact the undersigned at the telephone number provided below.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 4, 1997

By: _____

Ned A. Israelsen
Registration No. 29,655
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(619) 235-8550

NSB-4409:060497